

➔ Although often colloquially referred to as 'skin cancer', melanoma is a malignancy of melanocytes, which are the cells that produce pigment throughout the body, including in internal organs. The most frequently occurring form is cutaneous (skin) melanoma, but the disease can affect the eyes and, rarely, the digestive tract.

**EPIDEMIOLOGY**

Cutaneous melanoma occurs predominantly in fair-skinned populations. UV exposure is a major risk factor for the disease, and its increasing incidence over the past several decades might reflect our changing leisure habits: we are spending more time in the sun. Australia and New Zealand currently have the highest rates in the world (60 people in every 100,000 are diagnosed per year), with the USA (30 per 100,000 per year) and Scandinavia (20 per 100,000 per year) following.



**MECHANISMS**

The majority of melanomas are sporadic (without a heritable component) and have mutations that affect the p16<sup>INK4A</sup>-CDK4/CDK6-RB pathway, which results in aberrant cell-cycle control. Given that UV exposure is a significant risk factor, it is unsurprising that melanomas have the highest mutational load of all human cancers — most are UV-associated C>T and G>T transitions. However, mutations affecting the MAPK cascade are also common in melanoma, but are not necessarily UV-dependent.

**PREVENTION**



**SCREENING**

People with a family history and/or atypical naevi (moles) are recommended to undergo total-body skin examination. Although no randomized controlled study has shown an organized screening programme to reduce melanoma deaths, Germany introduced free screening after a non-randomized study resulted in reduced mortality.

**QUALITY OF LIFE**

Patient-reported outcomes are not always collected in current clinical trials, but they are gaining prominence — the patient's 'subjective' perception is crucial to understand the true benefit of treatment. In 2014, BRAF inhibitors were shown to positively affect quality of life outcomes in patients with stage IV melanoma.

**Rx MANAGEMENT**

For patients with localized disease, surgical removal is most often curative. However, if patients have a thick melanoma (Breslow's thickness >4 mm), the risk of death within 10 years can be as high as 50%. Although removal of cancer-positive lymph nodes (determined by biopsy) has been the global standard of care for >20 years, its role is changing owing in part to considerable morbidity. No available treatment has been internationally accepted in the adjuvant setting (after surgery) for patients at risk of recurrence; interferon has shown mixed results and is not used widely, and anti-angiogenesis drugs such as bevacizumab are also ineffective. For patients with metastatic disease, the benefit of surgical removal has only been proven for a single metastasis or for oligometastases that can be completely resected. Instead, systemic immunotherapies are offered: ipilimumab, which targets CTLA4, and nivolumab and pembrolizumab, which target PD1. BRAF and MEK inhibitors are also available, as single agents or in combination.

**OUTLOOK**

The future of melanoma research will focus on developing better treatments that can prolong survival and minimize adverse effects, as well as identify biomarkers that will accurately estimate prognosis and predict treatment outcomes. Next-generation immunotherapies, including new checkpoint inhibitors targeting PD1, are likely to be at the forefront of treatment. Experimental techniques such as adoptive cell transfer might be explored further.

